CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Express Mail Label No.: EL915578015US Date of Deposit: May 1, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Scott Stewart

#25
JRP
5/8/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Albert Z. ABRAM

Serial No.: 09/719,662

Filing Date: January 30, 2001

For: MOUSSE COMPOSITION

Examiner: C. Ostrup

Group Art Unit: 1614

CTO
5/19/03

DECLARATION OF RONALD HARDING

PURSUANT TO 37 C.F.R § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Ronald Harding, M.S., declare as follows:

1. I am Managing Director of E-Nova Research Pty Ltd, Australia. E-Nova is a product research and development company engaged in the management, design and development of new formulations for the pharmaceutical, personal care and household industries. My responsibilities include strategic direction, product design, project management, and formulation development. From September, 1995 to November, 2000 I was Research and Development Manager of Soltec Research Pty Ltd, Australia. Soltec is a product research and development company engaged in the design and development of new formulations for the pharmaceutical, personal care, animal health and household industries. My responsibilities at

pharmaceutical, personal care, animal health and household industries. My responsibilities at Soltec included coordinating with manufacturing, marketing and biological functions, developing new single and mixed fungicide formulations, and scale up studies of granular formulations. Prior to that, since 1978 I worked as a formulation chemist for both SHELL FORSCHUNG GmbH, Germany and SHELL RESEARCH Ltd, United Kingdom. My responsibilities included developing a novel insecticide/polymer mix, identifying practical manufacturing processes, providing technical support to business functions, and processing trials of new formulations up to manufacturing scale in plants.

2. I received a Master of Science in Colloid and Surface Chemistry in 1992 from the University of Bristol, Avon, United Kingdom. I graduated from the Royal Society of Chemistry -Part II from Mid Kent College of Further and Higher Education, Chatham, United Kingdom in 1988. I graduated from the Royal Society of Chemistry Part I from Mid Kent College of Further and Higher Education, Chatham, United Kingdom in 1986. I received a Higher National Certificate in Chemistry from Mid Kent College of Further and Higher Education, Chatham, United Kingdom, in 1982.

3. I have reviewed the specification of United States Patent Application Serial No. 09/719,662. I am not an inventor of the subject matter claimed. I have reviewed the rejections to the pending claims set forth in the Office Action mailed from the United States Patent and Trademark Office on November 1, 2002. I have reviewed the references cited by the Examiner as the subject of rejections regarding the patentability of the claimed invention. Specifically, I have reviewed Davis, U.S. Patent No. 5,143,717 (hereafter, "the '717 patent") and Woodford *et al.*, "Bioavailability and Activity of Topical Corticosteroids from a Novel Drug Delivery System, the Aerosol Quick-Break Foam", *J. Pharm. Sci.* 66 (1) (1977).

4. The '717 patent specification does not teach using organic solvents or cosolvents in amounts sufficient to solubilize the active ingredient. In Example 1, IPM is used as an emolient in an amount of 3.28%, and on page 8, IPM is listed as an emolient in a range of 0.98% to 4.46%. To the contrary, the present specification teaches specifically adding an organic cosolvent as follows:

> The composition further includes an organic cosolvent. The organic solvent may be an ester of a fatty acid, e.g. C12 –C15 alkyl benzoate, a medium to long chain alcohol, an aromatic and/or alkyl pyrollidinone, an aromatic and/or alkyl and/or cylic ketone, an aromatic and/or alkyl and/or cyclic ether, substituted and/or unsubstituted single or multiple ring aromatic, straight chain and/or branched chain and/or cyclic alkane or silicone.
>
> The cosolvent may be present in amounts of approximately 0.25% to 50%, preferably 0.5% to 2.0%. Preferred organic cosolvents include C12-C15 alkyl benzoates (Finsolv TN) and caprylic/capric triglyceride (Crodamol GTCC). (Specification, paragraph bridging pages 5-6.)

5. Claim 1 of the presently claimed invention requires an organic cosolvent. The language "the pharmaceutically active ingredient being solubilized in the composition but insoluble in both water and the occlusive agent" necessitates the presence of an organic cosolvent in an amount sufficient to solubilize the active ingredient.

6. An organic cosolvent is not required if a pharmaceutically active ingredient is suspended in a composition instead of being dissolved. Thus the stipulation that the composition comprise an organic cosolvent is essential for the invention, and it indicates that the active ingredient is dissolved in the composition. Stated differently, if an active agent is soluble in water or an occlusive agent such as petrolatum/mineral oil, then a cosolvent would not be required and would not be included in the composition.

7. The '717 Patent teaches an aerosolised antibiotic suspended in an oil in water emulsion. The specification teaches a suspension, specifically discussing micelles. There is no discussion or teaching of solvents.

8. Solubilized active ingredients are transported across the skin faster than active ingredients in a particulate (solid) form. Particularly in the case of corticosteroids, insufficient therapeutic activity is observed if the corticosteroid is delivered to the skin as a particulate when typical therapeutic doses are used.

9. Micelles are organized aggregates of surfactant molecules as explained in Colloid and Surface Chemistry, 4th Ed., Duncan Shaw submitted herewith as Appendix 1) and can form many shapes such as spheres, tubes, layers as aggregates, vesicles and lamella. Typically in less

concentrated solutions micelles form spherical aggregates or vesicles, which will are in the form of a dispersed phase within a continuous phase.

10. Woodford *et al.* teach using 2.0 g of a ***nonionic*** emulsifying wax (not "2.0g of non-emulsifying wax" as stated on page 4 of the Final Office Action in relation to U.S. Patent Application No. 09/719,662).

11. A non-ionic emulsifying wax is a suitable foaming agent for quick break foams such as the topical dosage corticosteroid quick break aerosol foam specifically described by Woodford *et al.* Especially in the presence of dichlorodifluoromethane and dichlorotetrafluoroethane, an aqueous alcohol system incorporating a non-ionic emulsifying wax may be used to prepare a quick break foam provided the alcohol-water ratio is between approximately 50:50 and 70:30.

12. The term "wax" is not synonymous with occlusion. Wax describes general physical properties and physical states (*See, e.g.*, Lenick, *et al.*, "Primary Ingredients" submitted herewith as Appendix 2). The generally accepted classification for oils, waxes and butters requires that the material be insoluble in water and have an appropriate physical state. An example of such a material is silicone wax 580 from Dow Corning. This material is insoluble in water, but is not occlusive as explained in the Dow Corning literature (submitted herewith as Appendix 3).

13. The formulations of Woodford *et al.* were occluded with a polyester film. Some sites were left nonoccluded, but these were protected by plastic to avoid the hydrating effect of occlusion.

14. Woodford *et al.* do not teach including an occlusive agent as claimed in the present application. Woodford *et al.* state that the actual nonionic emulsifying wax used was Polarwax A31 manufactured by Croda Chemicals. Information from Croda and the Cosmetic and Toiletries Bench Reference reveal that this wax is a mixture of cetostearyl alcohol and a polyoxyethylene derivative of a sorbitan fatty acid ester (*See* Appendix 4, submitted herewith). Neither a cetostearyl alcohol nor a polyoxyethylene derivative of a sorbitan fatty acid ester are considered occlusive agents. A polyoxyethylene derivative of a sorbitan fatty acid ester is a

medium to high HLB surfactant with good water affinity. Cetostearyl alcohol, although a long chain alkane, has a hydroxyl group attached at the end of the chain. This imparts significant polarity and hydrophilicity to the molecule. Hence, this property would allow easy transmission of water across a film made from this material. Although the wax (Polarwax) of Woodford *et al.* is precipitated onto the skin is not occlusive.

15. A polyester or food wrap film is often used when assessing the efficacy and bioavailability of an active ingredient in a composition. This type of cover provides occlusion, and the performance of active ingredients is normally enhanced when tested under occlusion. Woodford *et al.* use a polyester film for occlusion and not just as a protective barrier. In fact, Woodford *et al.* use a plastic guard to offer protection against external influences but not occlusion in a subsequent set of tests in the cited article.

16. A number of commercially available products use occlusion to achieve acceptable performance. Two such products, Emla Cream and Nicotine patches, use occlusive techniques to achieve efficacy. The consumer information sheet for Emla cream (submitted herewith as Appendix 5) stipulates the use of such a plastic food wrap or the like over the composition after application for this very purpose.

17. The mechanism of a quick break foam is well known. Woodford *et al.* describe the accepted mechanism as follows:

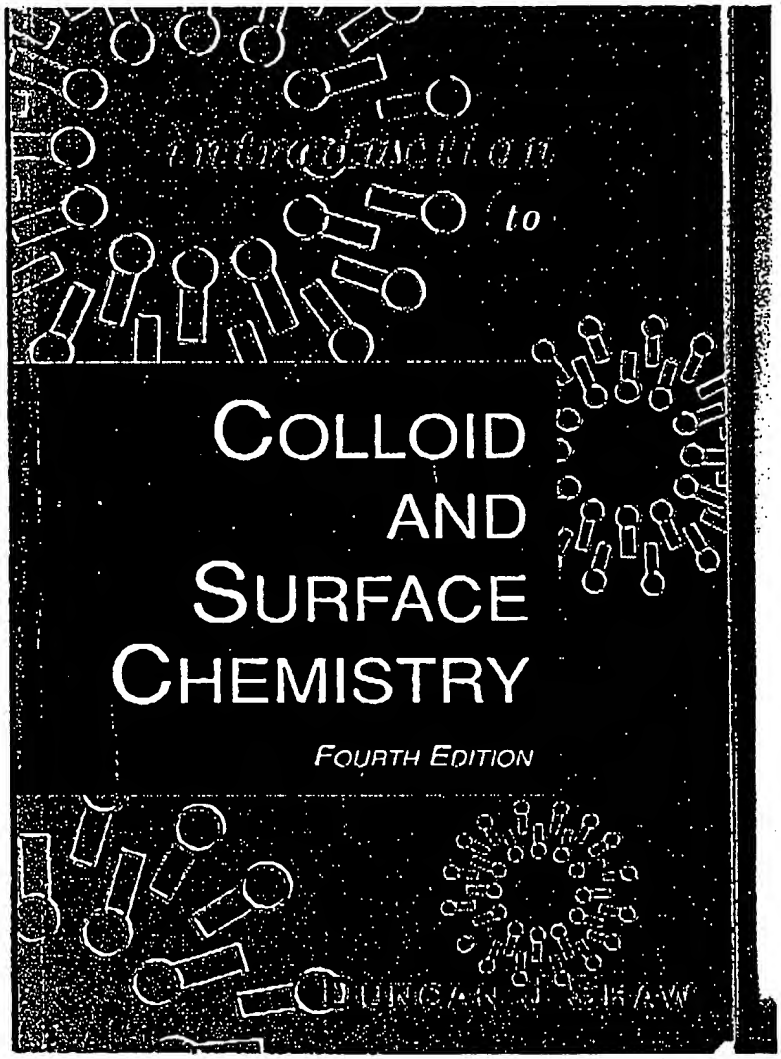
> "When the foam product is discharged from the container, the propellant is vaporized; the foaming agent (nonionic emulsifying wax) crystallized due to a loss of solubilizer (*i.e.*, propellant) and a reduction in temperature to below that at which the foaming agent deposited. The precipitation of the wax from solution produced a foam that collapsed on the skin as the wax redissolved at skin temperature".

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date

Ronald Harding, M.S.

Appendix 1


Introduction to
COLLOID AND SURFACE CHEMISTRY
FOURTH EDITION
DUNCAN J. SHAW

Electrophoretic deposition
Emulsion polymerisation
Food processing
Grinding
Heterogeneous catalysis
Ion exchange
Lubrication
Oil-well drilling
Sewage disposal
Soil conditioning
Sugar refining
Water clarification
Water evaporation control
Water repellency
Wetting

As can be seen from the second of these lists, the existence of matter in the colloidal state may be a desirable or an undesirable state of affairs, and so it is important to know both how to make and how to destroy colloidal systems.

Colloid science is very much an interdisciplinary subject, albeit with certain areas of physics and physical chemistry most prominent. Owing to the complexity of most colloidal systems, the subject often cannot be treated readily with the exactness that tends to be associated with much of these major subject areas. It is probably a combination of this lack of precision and its interdisciplinary nature, rather than lack of importance, that has been responsible in the past for an unjustifiable tendency to neglect colloid science during undergraduate academic training.

Until the last few decades colloid science stood more or less on its own as an almost entirely descriptive subject which did not appear to fit within the general framework of physics and chemistry. The use of materials of doubtful composition, which put considerable strain on the questions of reproducibility and interpretation, was partly responsible for this state of affairs. Nowadays, the tendency is to work whenever possible with well-defined systems (e.g. monodispersed dispersions, pure surface-active agents, well-defined polymeric material) which act as models, both in their own right and for real life systems under consideration. Despite the large number of variables which are often involved, research of this nature coupled with advances in the understanding of the fundamental principles of physics and chemistry has made it possible to formulate coherent, if not always comprehensive, theories relating to many of the aspects of colloidal behaviour. Since it is important that colloid science be understood at both descriptive and theoretical levels, the study of this subject can range widely from relatively simple descriptive material to extremely complex theory.

The natural laws of physics and chemistry which describe the behaviour of matter in the massive and molecular states also, of course, apply to the colloidal state. The characteristic feature of colloid science lies in the relative importance which is attached to the various physicochemical properties of the systems being studied. As we shall see, the factors which contribute most to the overall nature of a colloidal system are:

Particle size
Particle shape and flexibility
Surface (including electrical) properties
Particle–particle interactions
Particle–solvent interactions

Classification of colloidal systems

Colloidal systems may be grouped into three general classifications:

1. *Colloidal dispersions* are thermodynamically unstable owing to their high surface free energy and are irreversible systems in the sense that they are not easily reconstituted after phase separation.
2. *True solutions of macromolecular material* (natural or synthetic) are thermodynamically stable and reversible in the sense that they are easily reconstituted after separation of solute from solvent.
3. *Association colloids* which are thermodynamically stable (see Chapter 4).

Dispersions

The particles in a colloidal dispersion are sufficiently large for definite surfaces of separation to exist between the particles and the medium in which they are dispersed. Simple colloidal dispersions are, therefore, two-phase systems. The phases are distinguished by the terms *dispersed phase* (for the phase forming the particles) and *dispersion medium* (for the medium in which the particles are distributed) – see Table 1.1. The physical nature of a dispersion depends, of course, on the respective roles of the constituent phases; for example, an oil-in-water (O/W) emulsion and a water-in-oil (W/O) emulsion could have almost the same overall composition, but their physical properties would be notably different (see Chapter 10).

particularly useful when there is more than one surface-active species or unavoidable surface-active impurity present. In such cases surface tension measurements would probably be ambiguous.

Association colloids – micelle formation[48]

Physical properties of surfactant solutions

Solutions of highly surface-active materials exhibit unusual physical properties. In dilute solution the surfactant acts as a normal solute (and in the case of ionic surfactants, normal electrolyte behaviour is observed). At fairly well-defined concentrations, however, abrupt changes in several physical properties such as osmotic pressure, turbidity, electrical conductance and surface tension, take place (see Figure 4.13). The rate at which osmotic pressure increases with concentration becomes abnormally low and the rate of increase of turbidity with concentration is much enhanced, which suggests that considerable association is taking place. The conductance of ionic surfactant solutions, however, remains relatively high, which shows that ionic dissociation is still in force.

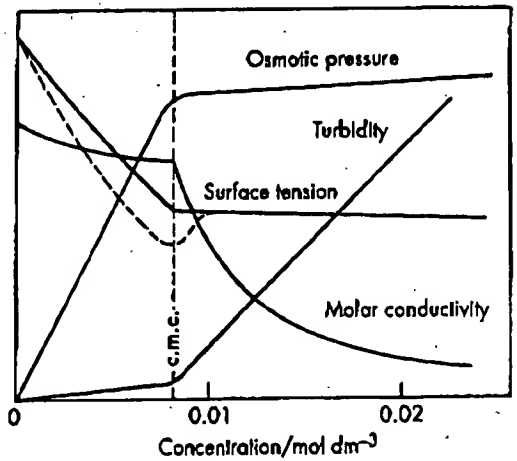


Figure 4.13 Physical properties of sodium dodecyl sulphate solutions at 25°C

McBain pointed out that this seemingly anomalous behaviour could be explained in terms of organised aggregates of *micelles*, of the surfactant ions in which the lipophilic hydrocarbon chains are orientated towards the interior of the micelle, leaving the hydrophilic groups in contact with the aqueous medium. The concentration above which micelle formation becomes appreciable is termed the *critical micelle concentration* (c.m.c.).

Micellisation is, therefore, an alternative mechanism to adsorption by which the interfacial energy of a surfactant solution might decrease.

When one considers the energetics of micellisation in terms of the hydrocarbon chains of the surfactant molecules, the following factors are among those which must be taken into account:

1. The intermolecular attractions between the hydrocarbon chains in the interior of the micelle represent an energetically favourable situation; but it is not one which is significantly more favourable than that which results from the alternative hydrocarbon–water attraction in the case of single dissolved surfactant molecules. Comparison of the surface tension of a typical hydrocarbon oil with the dispersion component of the surface tension of water (as discussed on page 67) illustrates this point.
2. Micellisation permits strong water–water interaction (hydrogen bonding) which would otherwise be prevented if the surfactant was in solution as single molecules wedged between the solvent water molecules. This is a most important factor in micelle formation and also of course, in any adsorption process at the aqueous interface. It is often referred to as the *hydrophobic effect*[49].

Experimental study of micelles

Critical micelle concentrations can be determined by measuring any micelle-influenced physical property as a function of surfactant concentration. In practice, surface tension, electrical conductivity and dye solubilisation measurements (see Figure 4.13 and page 90) are the most popular. The choice of physical property will slightly influence the measured c.m.c., as will the procedure adopted to determine the point of discontinuity.

Information concerning the sizes and shapes of micelles can be

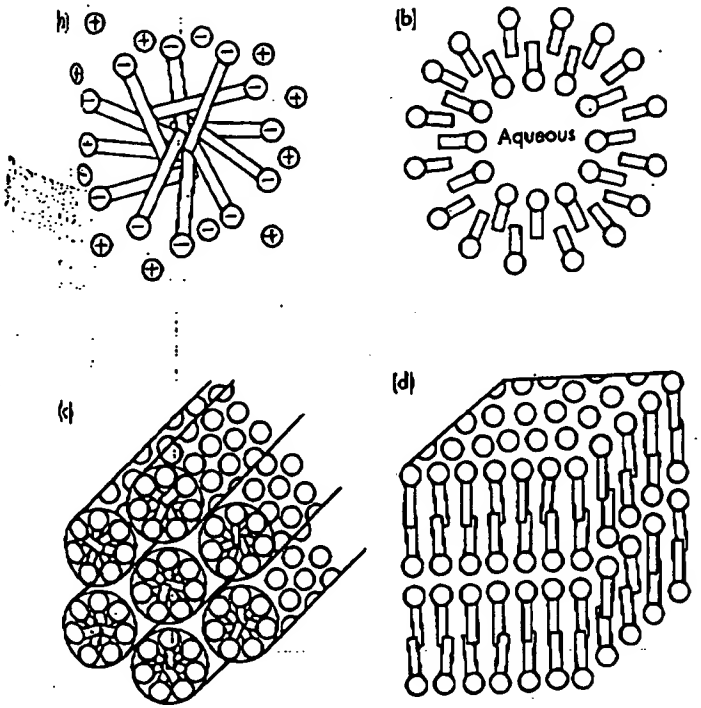


Figure 4.14 Micellar structures. (a) Spherical (anionic) micelle. This is the usual shape at surfactant concentrations below about 40 per cent. (b) Spherical vesicle bilayer structure (*see also Figure 4.28*), which is representative of the living cell. (c) and (d) Hexagonal and lamellar phases formed from cylindrical and laminar micelles, respectively. These, and other structures, exist in highly concentrated surfactant solutions

micelle, m, and the number of carbon atoms per hydrocarbon chain, n, are approximately related as follows:

n	12	14	16	18
m	33	46	60	78

Laminar and cylindrical models, in contrast, provide no satisfactory mechanism by which the size of the micelles might be limited.

3. For diffusion reasons, solubilisation (see next section) would not take place readily if the micelle were solid.

As mentioned above, the length of the surfactant's hydrocarbon chain will dictate the radius of a spherical micelle. This in turn determines the spacing of the outer polar groups. On this basis, for example, a dodecyl sulphate micelle surface would be expected to be approximately one-third sulphate groups and two-thirds hydrocarbon. The results of neutron scattering studies are consistent with this expectation. In an ionic micelle, the tendency of this hydrocarbon–water interfacial area to contract is balanced by head-group repulsion. Addition of electrolyte reduces this head-group repulsion, thus favouring an area per head-group that is smaller than the geometric optimum for a spherical micelle. Under such conditions, the micelle is likely to distort to a non-spherical shape.

There is evidence from nuclear magnetic resonance spectroscopy and partial molar volume measurements[153–154] which points to the possible existence of bound water in the micelle interior in the region of the first few CH_2 groups in from the polar head groups. The hydrocarbon interior of the micelle may, therefore, be considered in terms of an outer region which may be penetrated by water and an inner region from which water is excluded.

Solubilisation[51]

Surfactant solutions above the c.m.c. can solubilise otherwise insoluble organic material by incorporating it into the interior of the micelles; for example, the dye xylenol orange dissolves only sparingly in pure water but gives a deep red solution with sodium dodecyl sulphate present above its c.m.c.

The balance of electrostatic and hydrophobic interactions can be such as to cause the locus of solubilisation to be anywhere in the micelle from close to the surface to the inner core.

Solubilisation is of practical importance in the formulation of pharmaceutical and other products containing water-insoluble ingredients[51], detergency, where it plays a major role in the removal of oily soil (pages 166–176), emulsion polymerisation (page 17) and micellar catalysis of organic reactions[52].

In micellar catalysis, reactant must be solubilised at a location near to the micelle surface where it is accessible to reagent in the aqueous

Appendix 2

Dr. Z proudly presents

Primary Ingredients

by
Anthony J. O'Lenick, Jr.,
David C. Steinberg
and
Kenneth Klein

Table of Contents

Table of Contents (cont'd)

1. Borgae oil
2. Linseed oil

Table of contents (cont'd)

3. Castor oil
4. Veronia oil

Class VI I Products having unusual components (cont'd)

5. Carnuba
6. Tung oil
7. Jojoba oil
8. Candelilla
9. Ongokea oil

Conclusion

Preface

This book was written to provide timely salient information to the formulator of personal care products that use fats, oils, triglycerides, waxes, butters or their surfactant derivatives in formulations. In short this definition includes most formulators of personal care products. We have given information on many materials, including chemical data, source data, availability and carbon distribution data. By no means is this list exhaustive or all inclusive. It is intended to be illustrative of the type of materials available.

We encourage the reader to consider not only the oil described, but also the implication of the choice of oil upon performance of surfactant and other derivatives.

Dr. Z.

Background

The skin and hair are major areas which oil may be applied for a beneficial effect. The exact benefit of the oil application depends in great part upon the particular oil chosen.

Oils that have a very dry feel, which we classify as ultra light oils, find applications in sunscreen applications and massage oil where a non-greasy feel is very critical to product aesthetics. This class of oils also finds application in aromatherapy.

Oils, Fats, Waxes, and Butters

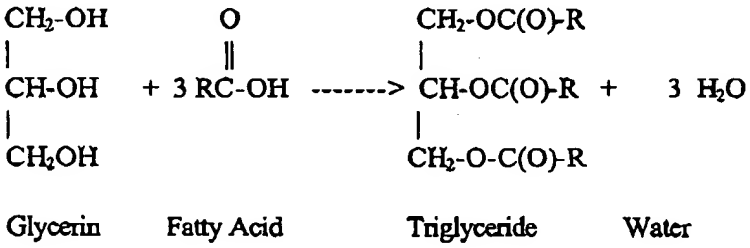
The terms oils, fats, butters and waxes have been misused over the years. The historical definition of wax has previous been given. Butters, oils and fats are all triglycerides. Fats have a titer point of over 40.5 ° C, oils have a titer point of below 40.5 ° C. Butters have a titer below 40.5 ° C but above 20 ° C. Oils are liquid at room temperature and we now use this word to describe any compound that is a liquid and is insoluble in water. As a result, Jojoba is referred to as an oil, despite the fact it is really a liquid wax.

Because oils, fats, butters and waxes are complex mixtures of homologues of similar chemical structures, it is difficult to obtain a true melting point. As the lower molecular weight fractions melt, they act as solvents to dissolve the higher molecular weight products. This results in a very wide melting "range" for these compounds. For this reason, titer point is generally determined on fats, oils, waxes and butters.

The titer is defined as the re-solidification point of the melted oil, fat butter or wax. The procedure is to heat the product to be tested until it is completely liquid, then to slowly cool with stirring. This is done until the temperature stays constant for 30 seconds, or begins to rise. The titer point is the highest temperature indicated by this rise.[1]

Triglycerides

Triglycerides are the tri-ester of glycerin with three equivalents of organic acid. Fatty acids are defined as those acids having alkyl or alkylene groups being C-5 and higher. The reaction is as follows:

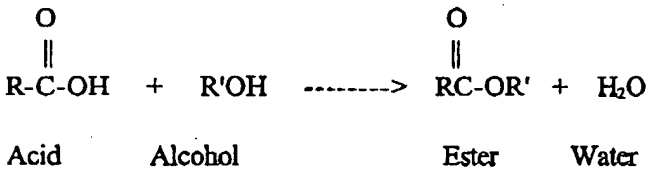


When the triglyceride is saponified to make a surfactant, such as soap, glycerin is liberated. When a wax is saponified, a fatty alcohol is liberated. This makes the type of products that can be made using the two types of materials quite different. Saponification is a general term to define the chemical reaction that breaks the ester linkage. Glycerine, produced as a by-product of saponification is water soluble and fatty insoluble. The fatty alcohol produced as a by-product of the saponification of a wax is water insoluble and generally fatty soluble.

Waxes Esters

Wax esters are defined as esters of long chained acids that have been reacted with long chained alcohols. Other chemicals are called waxes if they possess tactile properties similar to a true wax such as beeswax. Polishes are a major application area for this class of materials.

Wax esters have two fatty groups. One is contained in the alcohol portion of the molecule, the other is in the acid group. Esters are synthesized by the reaction of an organic acid with and an organic alcohol. Esterification is the reverse of saponification, in that ester linkages are formed.

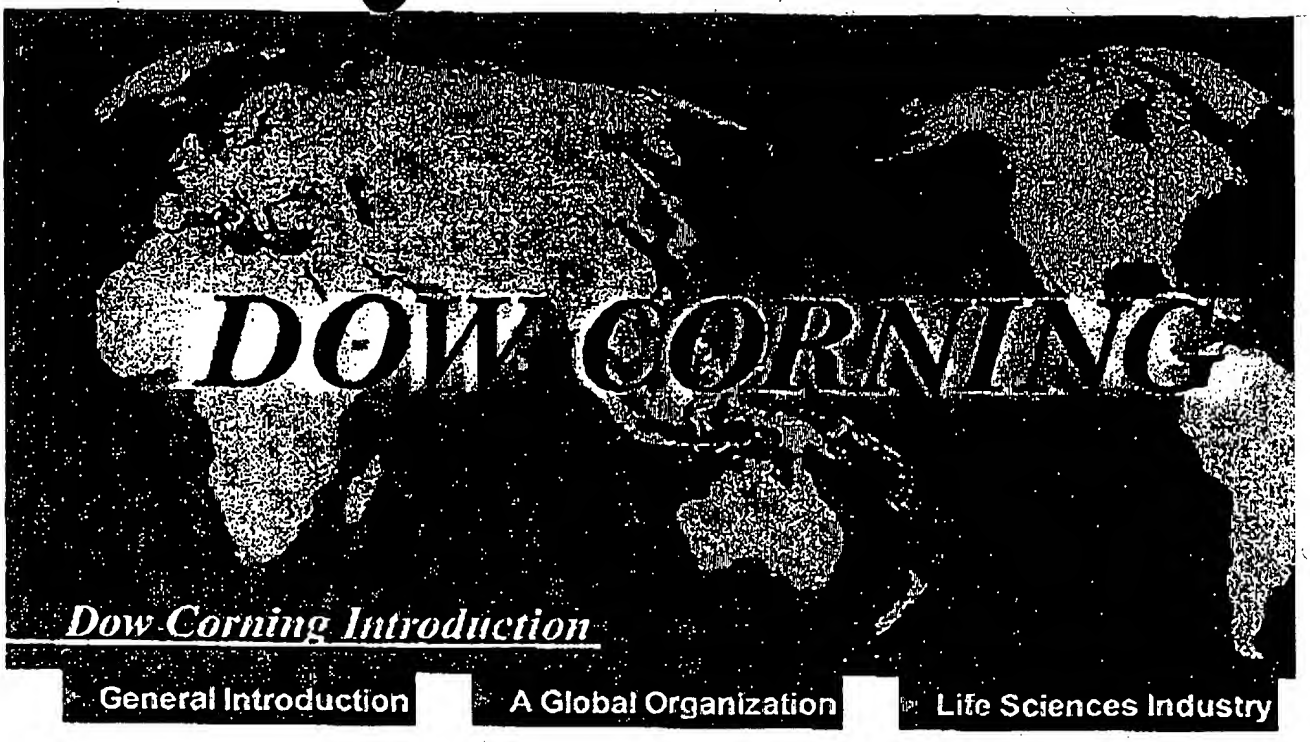


Not only is the fatty alcohol that is formed during saponification not water-soluble, many naturally occurring waxes also contain other components, like hydrocarbon resins, which are likewise water insoluble and quite inert to chemical reaction. This needs to be considered when using these materials.

CTFA Nomenclature

CTFA now requires the genus and species of the plants or insects that produce a given wax, oil, butter or fat and all products which are derived from the various oils, fats, butters and waxes. This is due, in part, to the European Union's use of the Latin names for ingredient listings. This information is very helpful to the formulator in understanding the source of the fatty portion of the surfactant.

Appendix 3


DOW CORNING
Dow Corning Introduction
General Introduction
A Global Organization
Life Sciences Industry

Specifications writers: These values are not intended for use in preparing specifications. Please contact your local Dow Corning sales representative prior to writing specifications on this product.

Introducti n

Product Name	580
Product Family	Alkylmethylsiloxane
INCI Name	Stearoxytrimethylsilane (and) Stearyl Alcohol
Description	Mixture of Trimethylsiloxy Stearate and Stearyl Alcohol
Benefits	* Lubricity * Provides water repellent, non-occlusive film * Detackification
Main Application	Skin Cream
Use Levels	0.5-10%
Appearance	Soft, semicrystalline wax
Functionality	$C_{18}H_{37}$ and Stearyl Alcohol
Melting Point Avg (degree C)	~48
Average Molecular Weight	300
Melt Viscosity @40 degrees C (cst)	NA
Refractive Index @78 degrees C	NA
Specific Gravity @25 degrees C	1

Polawax provides a simple, convenient and economical means of preparing emulsions containing high levels of electrolytes/ionic materials. In addition, its performance is unaffected by the presence of most cosmetic and pharmaceutical active ingredients.

Polawax possesses excellent heat stability and is recommended for the preparation of creams and lotions which require autoclaving. Polawax exhibits no loss in performance on heating to 150°C for two hours. There is only minor deterioration in colour with a 2 – 3% loss in weight and a slight hardening of the wax.

Polawax A31. This is a special grade of Polawax developed for use in aerosols. It shows improved solubility in aqueous alcohol and the usual halogenated hydrocarbons aerosol propellants, and is therefore ideal for use in quick–breaking foams.

Quick–breaking foams are clear, single phase systems which produce a light, collapsible foam when dispensed. A standard formulation contains 1 –4% Polawax A31 in an aqueous alcoholic medium with a suitable solubilising propellant.

January 1990

Croda

Croda Surfa tants Pty Ltd PO Box 1012 Richmond North Victoria 3121 Australia
Tel (03) 429 4422 Telex 31733 Fax (03) 427 0327
Sydney Offic PO Box 365 Liverpool NSW 2170 Australia
Telephone (02) 602 4922 Fax (02) 602 1632

Polawax

Appendix 4

Nonionic emulsifying wax

Polawax is a nonionic emulsifying wax which produces smooth and stable oil in water emulsions. Three grades are available.

Polawax GP200 – a general purpose self emulsifying wax.

Polawax A31 – a grade developed for use in aerosol quick breaking foams.

Polawax NF – a general purpose self–emulsifying wax conforming to United States National Formulary specifications.

Analytical details	Polawax GP200	Polawax A31	Polawax NF
Acid value	1.8 max	2.0 max	1.0 max
Saponification value	7.8 – 15	7.5 – 12.5	9.0 – 12.5
Drop point °C	47 – 52	43 – 50	47 – 53

The analytical details given here are intended only as a guide and do not constitute a purchasing specification.

Safety in use. Polawax has been subject to the following physiological tests. Copies of the relevant reports are available on request; their conclusions are summarised here.

LD_{50} (oral):
The acute lethal dose to rats was found to be greater than 16g/kg body weight.

Irritant effect on rabbit skin:
Polawax cannot be considered a primary irritant.

Irritant effect on rabbit eye mucosa:
Polawax cannot be considered an irritant to the eye according to the CFR definition.

Properties. Polawax is a self bodying emulsifier which can be used to manufacture emulsions ranging from mobile liquids to rigid solids. It is suitable for the emulsification of oils, fats and waxes and for the preparation of powder suspensions. In cosmetic and pharmaceutical preparations, Polawax has proved to be superior to many emulsifiers, including glycerol monostearate and diethylene glycol monostearate.

.../2

Croda Surfactants Pty Ltd PO Box 1012 Richmond North Victoria 3121 Australia
Tel (03) 429 4422 Telex 31733 Fax (03) 427 0327
Sydney Office PO Box 365 Liverpool NSW 2170 Australia
Telephone (02) 602 4922 Fax (02) 602 1632

Water for Irrigation, Sterile—*see Water for Irrigation, Sterile USP*

Water, Purified—*see Water, Purified USP*

Carnauba Wax

» Carnauba Wax is obtained from the leaves of *Copernicia cerifera* Mart. (Fam. Palmae).

Packaging and storage—Preserve in well-closed containers.

Melting range, *Class II* (741): between 80° and 86°.

Acid value—Weigh accurately 3 g into a 250-mL flask attached to a reflux condenser, add 50 mL of a mixture of isopropyl alcohol and toluene (5:4), and boil gently until the wax is completely dissolved. Remove the flask from the condenser, add about 1 mL of phenolphthalein TS, and immediately titrate with 0.5 N alcoholic potassium hydroxide VS to a faint, reddish yellow color. [NOTE—Do not allow solution to cool; titrate at warm temperature after refluxing.] Calculate the acid value as the number of mg of potassium hydroxide required to neutralize the free acids in 1 g of Carnauba Wax. The acid value so obtained is between 2 and 7.

Saponification value (401)—To the solution from the test for *Acid value* add 15.0 mL of 0.5 N alcoholic potassium hydroxide VS, reflux for 3 hours, and titrate the excess alkali with 0.5 N hydrochloric acid VS to a yellow-amber color. Perform a blank determination (see *Residual Titrations* under *Titrimetry* (541)). The saponification value is the summation of the ester value so obtained and the *Acid value*, and it is between 78 and 95.

Residue on ignition (281)—Heat 2 g in an open porcelain or platinum dish over a flame: it volatilizes without emitting an acrid odor. Ignite: the weight of the residue does not exceed 5 mg. Not more than 0.25% is found.

Heavy metals, *Method II* (231): 20 µg per g.

Organic volatile impurities, *Method IV* (467): meets the requirements.

Emulsifying Wax

» Emulsifying Wax is a waxy solid prepared from Cetostearyl Alcohol containing a polyoxyethylene derivative of a fatty acid ester of sorbitan.

Packaging and storage—Preserve in well-closed containers.

Melting range (741): between 50° and 54°, the following method being used. Melt a quantity of the test substance slowly, while stirring, until it reaches a temperature of 90° to 92°, remove the source of the heat, and allow the molten substance to cool to a temperature of 8° to 10° above the expected melting point. Chill the bulb of a suitable thermometer (see *Thermometers* (21)) to 5°, *wipe it dry, and while it is still cold, dip it into the molten substance so that the bulb is completely covered. Withdraw it immediately, and hold it vertically away from the heat until the surface dulls. Fix the thermometer securely in a test tube so that the lower point is 15 mm from the bottom of the test tube. Place the test tube in a water bath at 10° to 15° and allow it to remain at that temperature for 30 minutes. Raise the temperature of the bath at the rate of 2° per minute to 30°, then change to a rate of 1° per minute, and note the temperature at which the first drop of melted substance leaves the thermometer. Repeat the determination twice on a freshly melted portion of the test substance. If the variation of three determinations is less than 1°, take the average of the three as the melting point. Otherwise, make two additional determinations, and take the average of the five.*

Hydroxyl value (401): between 178 and 192.

Iodine value (401): not more than 3.5.

Saponification value (401): not more than 14.

pH (791): between 5.5 and 7.0, in a dispersion prepared by heating a mixture of 3 g of it in 100 mL of water to 55°, with stirring, followed by cooling to 25°.

Microcrystalline Wax

» Microcrystalline Wax is a mixture of straight-chain, branched-chain, and cyclic hydrocarbons, obtained by solvent fractionation of the still bottom fraction of petroleum by suitable dewaxing or deoiling means.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate the name and proportion of any added stabilizer.

Color—Melt about 10 g on a steam bath, and pour 5 mL of the liquid into a clear-glass, 16- × 150-mm bacteriological test tube: the warm, melted liquid is not darker than a solution made by mixing 3.8 mL of ferric chloride CS and 1.2 mL of cobaltous chloride CS in a similar tube, the comparison of the two being made in reflected light against a white background, the tubes being held directly against the background at such an angle that there is no fluorescence.

Melting range, *Class III* (741): between 54° and 102°.

Consistency—

Apparatus—Determine the consistency of Microcrystalline Wax by means of a penetrometer fitted with a polished metal needle weighing 2.5 ± 0.05 g and having a truncated symmetric tapered angle of 9°10′ ± 15′. The needle is tapered, with a length of 25.4 mm, and the shaft attached to the needle is 58 mm in length and 3.17 mm in diameter. The plunger that fits into the penetrometer and guides the path of the needle weighs 47.5 ± 0.05 g. An additional weight of 50 ± 0.05 g is added to the top of the plunger to give a total load of 100 g.

Procedure—The wax specimen is cast in a brass cylinder open at both ends. The cylinder has an inside diameter of 25.4 mm and is 31.8 mm in height. Place the cylinder on a brass plate wetted with an equal volume mixture of glycerin and water, and place the plate on two corks. Pour the wax, melted at approximately 17° above its congealing point, into the cylinder. Continue pouring the wax until a convex meniscus is formed above the cylinder. Allow the specimen to cool for 1 hour at approximately 24°. Shave excess wax from the top of the cylinder, and remove the plate. With the smooth wax surface in the up position, condition the specimen in a water bath at 25° for 1 hour.

Arrange the penetrometer so that the wax specimen is completely immersed in the water bath while penetration is run. Lower the needle until the tip just touches the top surface of the specimen. Release the needle for 5 seconds, and read the depth of penetration in tenths of millimeters. Perform four determinations, and calculate the average value of the four readings. The consistency value of Microcrystalline Wax is between 3 and 100 (not less than 0.3 mm and not more than 10.0 mm).

Acidity—If the addition of phenolphthalein TS in the test for *Alkalinity* produces no pink color, add 0.1 mL of methyl orange TS: no red or pink color is produced.

Alkalinity—Introduce 35 g into a 250-mL separator, add 100 mL of boiling water, and shake vigorously for 5 minutes. Draw off the separated water into a casserole, wash further with two 50-mL portions of boiling water, and add the washings to the casserole. To the pooled washings add 1 drop of phenolphthalein TS, and boil: the solution does not acquire a pink color.

Emla®

ELEMENTI PER L'IDENTIFICAZIONE DEL MEDICINALE

Denominazione del medicinale
EMLA®

Composizione
Un grammo di crema contiene:
Principi attivi:
lidocaina mg 25; prilocaina mg 25.
Eccipienti: olio di ricino idrogenato poliossietilenato, polimero dell'acido acrilico, sodio idrossido, acqua depurata.

Forma farmaceutica e contenuto delle confezioni
Crema per uso esterno.

Confezioni
Scatola contenente un tubetto da 5 g di crema + 2 cerotti occlusivi.
Scatola contenente 5 tubetti da 5 g di crema + 10 cerotti occlusivi.
Scatola contenente un tubetto da 30 g di crema.

Categoria farmacoterapeutica
ATC
N01BB20 Anestetici locali amidi in associazione.

Titolare dell'autorizzazione all'immissione in commercio
Astra Farmaceutici S.p.A. - Via Messina, 38 - 20154 Milano.

Prodotto, confezionato e controllato da:
Astra Pharmaceutical Production AB - Södertälje (Svezia).

Indicazioni terapeutiche
Analgesia superficiale della cute in concomitanza di interventi chirurgici superficiali, inserzione di cateteri e.v..
Analgesia superficiale della mucosa genitale in concomitanza di interventi chirurgici superficiali o di anestesia per infiltrazione.

INFORMAZIONI CHE DEVONO ESSERE CONOSCIUTE PRIMA DELL'USO DEL MEDICINALE

Controindicazioni
Ipersensibilità agli anestetici locali di tipo amidico o agli altri componenti o altre sostanze strettamente correlate dal punto di vista chimico.
Metaemoglobinemia congenita o idiopatica. Dermatite atopica.
Controindicato in gravidanza, durante l'allattamento e nei bambini fino a 6 mesi di età.

Opportune precauzioni d'impiego
EMLA® crema non deve essere applicata sulle ferite, sulle mucose genitali dei bambini o sulle aree affette da dermatite atopica. Qualora fosse richiesta l'applicazione in prossimità degli occhi, occorre usare particolare cautela per il rischio di irritazioni corneali.

Interazioni con altri medicinali ed interazioni di qualsiasi altro genere
EMLA® crema può accentuare la formazione di metaemoglobina in pazienti trattati con altri farmaci noti per indurre metaemoglobinemia (sulfonamidi).
Nel caso fosse necessaria l'applicazione di grandi quantità di EMLA® crema, occorre valutare attentamente il rischio di tossicità sistemica aggiuntiva nei pazienti già in trattamento con altri anestetici locali o farmaci a struttura chimica correlata (tocainide).

Avvertenze speciali
Lidocaina e prilocaina attraversano la barriera placentare e passano al feto; esse vengono escrete nel latte materno. Nelle pazienti che allattano occorre decidere se rinunciare a nutrire al seno il lattante ed iniziare il trattamento o, viceversa, proseguire l'allattamento evitando la somministrazione del medicinale.
Il trattamento con EMLA® crema deve essere evitato nei prematuri e nei bambini fino a 6 mesi di età.
Non sono noti effetti sulla capacità di guidare autoveicoli o di azionare macchinari.
Tenere fuori dalla portata dei bambini.

ISTRUZIONI NECESSARIE E CONSUETE PER UNA CORRETTA UTILIZZAZIONE

Dose, modo e tempo di somministrazione
Uso esterno.

Cute
Applicare sulla cute uno strato spesso e coprire con bendaggio occlusivo (un apposito cerotto è accluso alle confezioni da 5 g). In generale, si raccomanda una dose di crema pari a 1,5 g ogni 10 cm^2. L'applicazione deve essere effettuata da 1 a 3 ore prima dell'intervento sulla cute. La crema va rimossa in concomitanza della procedura operativa, l'effetto anestetico perdura per almeno un'ora.
Procedure dermatologiche minori (ad es. venipuntura o chirurgia su aree ristrette): applicare circa 2 g di crema (mezzo tubetto della confezione da 5 g) per almeno 1 ora prima dell'intervento.
Procedure dermatologiche su aree estese (ad es. dermoabrasione): applicare uno strato spesso di crema (1,5-2 g ogni 10 cm^2) per almeno 2 ore prima dell'intervento.
Bambini di età compresa tra 6 e 12 mesi: la dose totale non deve superare i 2 g su un'area totale non superiore a 16 cm^2. Applicare un'ora prima della procedura dermatologica e coprire con bendaggio occlusivo. Il tempo di applicazione non deve superare le 4 ore.

Mucosa genitale
Applicare su tutta l'area interessata, incluse le pliche mucosali, una dose variabile da 5 a 10 g di crema secondo il numero e l'ampiezza delle lesioni da trattare (ad es. condilomi) per circa 10 minuti prima dell'intervento chirurgico. Non è necessario coprire con bendaggio occlusivo. L'intervento deve iniziare immediatamente dopo la rimozione della crema.
VEDERE ISTRUZIONI PER L'USO (FIGURE 1-6).

Modalità di intervento in caso di dose eccessiva
Ad eccezione di un caso di metaemoglobinemia (vedere Effetti indesiderati) non sono stati segnalati altri casi di tossicità sistemica.
Nell'eventualità di intossicazione dopo applicazione di EMLA® crema, gli effetti sistemici dovrebbero essere analoghi a quelli indotti con altre vie di somministrazione.
La tossicità degli anestetici locali si manifesta con sintomi di eccitazione del sistema nervoso e, nei casi più gravi, con depressione del sistema nervoso centrale e cardiovascolare. I sintomi neurologici (convulsioni, depressione del SNC) devono essere trattati mediante assistenza respiratoria e somministrazione di anticonvulsivanti.
La metaemoglobinemia può essere trattata con blu di metilene iniettato lentamente per via endovenosa.
Dal momento che l'assorbimento attraverso la cute è lento, il paziente che accusa sintomi di intossicazione deve essere tenuto in osservazione per alcune ore dopo il trattamento d'emergenza. Non sono stati riferiti casi di assunzione di EMLA® crema per via orale.

Effetti indesiderati
Le reazioni più comuni sono di carattere locale, quali pallore transitorio, eritema (arrossamento). Solo occasionalmente sono stati segnalati casi di edema e sensazione di bruciore all'inizio dell'applicazione. Alte dosi di prilocaina possono causare un aumento dei livelli di metaemoglobina (è stato segnalato un caso di metaemoglobinemia in un bambino di tre mesi trattato contempo-

raneamente con sulfonamidi ed EMLA® crema). In casi molto rari, l'applicazione locale dei preparati a base di anestetici ha causato reazioni allergiche (nei casi più gravi shock anafilattico).
SI INVITA IL PAZIENTE A COMUNICARE AL PROPRIO MEDICO QUALSIASI EFFETTO INDESIDERATO DIVERSO DA QUELLI SOPRA INDICATI.

Scadenza e precauzioni per la conservazione
Conservare a temperatura ambiente. Chiudere accuratamente il tubetto dopo l'uso.

ATTENZIONE: NON UTILIZZARE IL MEDICINALE DOPO LA DATA DI SCADENZA INDICATA SULLA CONFEZIONE.

DATA DELL'ULTIMA REVISIONE DEL PRESENTE DOCUMENTO DA PARTE DEL MINISTERO DELLA SANITÁ: 12.02.97.

ISTRUZIONI PER L'USO

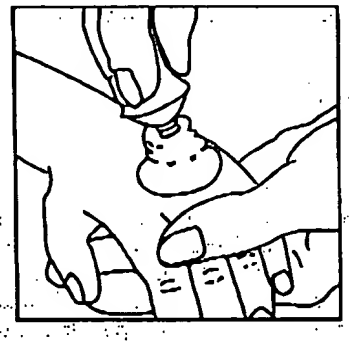


Figura 1
Applicare uno spesso strato di crema (1,5-2,5 g) in corrispondenza del sito da trattare.

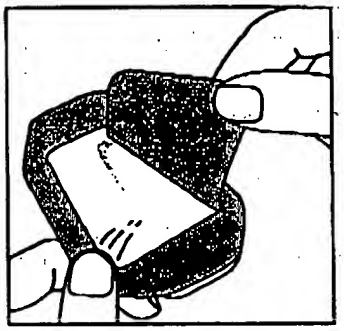


Figura 2
Prelevare un cerotto per il bendaggio protettivo e rimuovere la parte centrale.

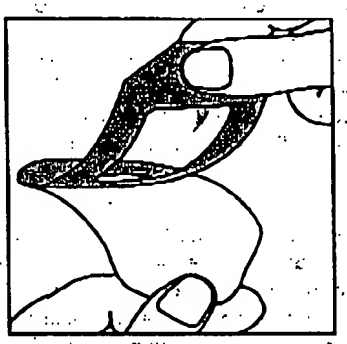


Figura 3
Asportare la carta posta a protezione dello strato adesivo.

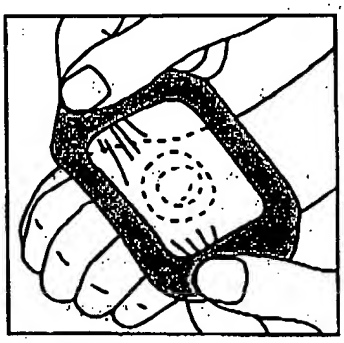


Figura 4
Coprire lo strato di EMLA® evitando che oltrepassi i bordi del cerotto. Premere con cura il contorno del cerotto, assicurandosi che non ci siano perdite di crema.

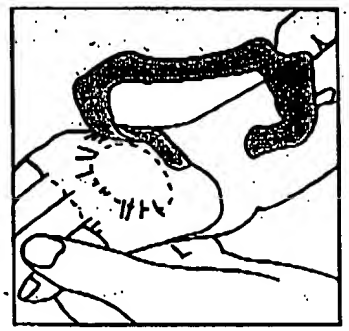


Figura 5
Rimuovere la restante carta di supporto dal bordo del cerotto. L'ora di applicazione può essere annotata direttamente sul bendaggio.
EMLA® deve essere applicata almeno un'ora prima dell'intervento: l'applicazione potrebbe continuare per numerose ore senza perdita di efficacia.

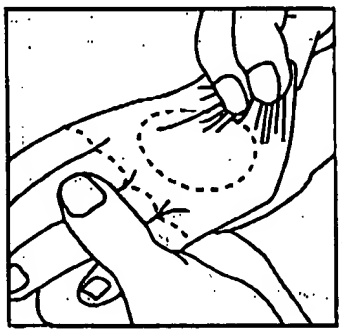


Figura 6
Rimuovere il bendaggio protettivo, eliminare la crema e pulire il sito da trattare. La durata dell'effetto anestetico è di almeno un'ora dopo la rimozione del bendaggio.

Consumer Medicine Information Consum r Medicine Information <<EMLA>> ® Cream Prilocaine 2.5%, lignocaine 2.5%, Cream What is in this leaflet
This leaflet answers some of the common questions people ask about <<EMLA>> Cream. It does not contain all the information that is known about <<EMLA>> Cream.

It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor will have weighed the risks of you taking <<EMLA>> Cream against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine. You may need to read it again.
What <<EMLA>> Cream is used for
<<EMLA>> Cream is used as a local anaesthetic (i.e. for pain relief) on the skin prior to procedures.

These procedures may include taking blood samples, skin grafting, cleaning leg ulcers or inserting intravenous catheters.
How <<EMLA>> Cream works
<<EMLA>> is a mixture of two local anaesthetics, lignocaine and prilocaine.

These local anaesthetics are combined with special agents which allow the products to pass through the skin. Once through the skin the numbing effect they produce allows minor surgical procedures to be done without you feeling any pain. However you may still experience sensations such as pressure and touch in this area.

<<EMLA>> Cream is not addictive.
Before you use <<EMLA>> Cream When you must not use it
Do not use <<EMLA>> Cream on areas with an infection, skin rash, cuts, grazes or other open wounds, with the exception of leg ulcers. If any of these problems are present, check with your doctor or pharmacist before using <<EMLA>> Cream.

If you are going to have a vaccine, tell the doctor or nurse that you have used <<EMLA>> . They can ensure that the specific vaccine you are to receive can be used together with <<EMLA>> .

Do not use <<EMLA>> Cream on pre-term newborn infants.

Do not use <<EMLA>> Cream near the eyes, as it may cause some irritation. If <<EMLA>> does accidentally get into your eyes, immediately rinse them with large amounts of luke warm water and contact your doctor or pharmacist.

<<EMLA>> Cream should not be applied inside the ear to the eardrum.

If you are pregnant or breast-feeding you should always be very careful with the use of medicines. <<EMLA>> has not been shown to have any harmful effects in these situations. Even so, you should always check with your doctor before using any medicine during pregnancy or breast-feeding.

Do not use after the use by (expiry) date printed on the pack. It may have no effect at all, or worse, an entirely unexpected effect if you use it after the expiry date.

Do not use <<EMLA>> if the packaging is torn or shows signs of tampering.

Do not use it to treat any other complaints unless your doctor says it is safe.
Before you start to use it You must tell your doctor or pharmacist about any of these:

Allergies you have to any:

Ingredients listed at the end of this leaflet

Local anaesthetic, for example those used at the dentist

Adhesives or sticking plasters.

If you have an allergic reaction, you may get a skin rash, hay fever or an asthma attack.

Any of these medical conditions:

dermatitis

methaemoglobinaemia.

It may not be safe for you to use << EMLA>> Cream if you have either of these conditions.

Care should be taken when applying << EMLA>> Cream to patients with Atopic dermatitis. A shorter application time, 15-30 minutes, may be sufficient. When mollusca are removed from the skin in children with atopic dermatitis, a 30 minutes application time is recommended.
Taking other medicines Tell your doctor or pharmacist if you are taking any other medicines, including:

a sulphonamide antibiotic e.g. co-trimoxazole

medicines that you buy at your pharmacy, supermarket or health food shop.

These medicines may affect the way << EMLA>> works.
Using << EMLA>> Cream How to use it
Be sure to follow the instructions in the pack on how to apply << EMLA>> Cream carefully.

Apply a thick layer of << EMLA>> Cream to the skin under an airtight dressing such as Tegaderm® or plastic food wrap.
On skin:
Adults: For minor skin procedures (e.g. needle insertion and surgical treatment) apply approximately ½ tube (2 g) for a minimum of 1 hour, maximum 5 hours. For larger procedures (e.g. skin grafting) apply 1.5-2 g/10 cm2 for a minimum of 2 hours, maximum 5 hours.

Children: Minor skin procedures (e.g. needle insertion and surgical treatment), apply approximately 1 g/10cm2, application time approximately 1 hour.

Neonates under the age of 3 months: Apply up to 1 g of Cream on a skin area no larger than 10 cm2.

Infants between 3 and 11 months of age: Apply up to 2 g of Cream on a total skin area of no larger than 20 cm2. Application time approximately 1 hour and not more than 4 hours.

Children between 1-5 years: Apply up to 10 g of Cream on a skin area no larger than 100 cm3.

Children between 6-11 years: Apply up to 20 g of Cream on a total skin area no larger than 200 cm2.
Leg ulcers:
Leg ulcers in adults: Apply a thick layer of Cream approximately 1-2 g/10 cm2 up to a total of 10 g to the leg ulcer. Cover with an air-tight dressing. The application time should be at least 30 minutes, but up to 60 minutes may improve the anaesthesia further. Cleansing should start without delay after the removal of the Cream. Remove the Cream with cotton gauze.

Things you must do

Remember to apply << EMLA>> on intact skin at least one hour before your procedure is due. For leg ulcers remember to apply << EMLA>> 30 minutes before your ulcer is due to be cleaned. Tell your doctor exactly when you put << EMLA>> on. If you do not, the procedure may hurt more than it would otherwise.

If you are using << EMLA>> on leg ulcers, only use the tube once. Throw out any cream left in the tube after use.

Things to be careful of

Do not use << EMLA>> Cream on leg ulcers for longer than 2 months without checking with your doctor or pharmacist.

Make sure the dressing covering the Cream is firmly fixed, especially on young children. If << EMLA>> is not covered carefully it may not work effectively.

If you forget to use it

Apply << EMLA>> as soon as you realise, if it is less than one hour until you are supposed to have the procedure. Tell your doctor exactly when you put << EMLA>> on and they will decide when the procedure can take place.

Overdose

With the recommended doses of << EMLA>> , no toxic effects have been reported. However, if you use too much << EMLA>> you will probably feel nervous, dizzy, have blurred vision and shaky hands.

Telephone your doctor or the National Poisons and Hazardous Chemicals Information Centre (Ph: 0800 POISON or 0800 764 766) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too much << EMLA>> Cream. Even if there are no signs of discomfort or poisoning.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are using << EMLA>> .

A mild reaction (paleness or redness of the skin, slight puffiness, initial burning or itching) may occur on the area on which << EMLA>> Cream is used. These are normal reactions to the anaesthetics and will disappear in a short while without any measures being needed.

If any of the following happen, remove << EMLA>> and tell your doctor immediately or go to Accident and Emergency at your nearest hospital:

a rash at a spot where << EMLA>> is not being used

difficulty with breathing.

If you have them, you may have a serious (allergic) reaction to << EMLA>> . You may need urgent medical attention or hospitalisation. These side effects are very rare.

Some people may get other side effects while taking << EMLA>> .

Important: This leaflet alerts you to some of the situations when you should call your doctor. Other situations, which cannot be predicted, may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using << EMLA>> .

After using it Storage

Keep your cream in the pack until it is time to use it.

If you squeeze << EMLA>> out of the tube it will not keep well.

Keep it in a cool dry place where the temperature stays below 30°C. Do not let it freeze.

Do not store it or any other medicine in the bathroom or near a sink.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it. A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Do not leave it in the car on hot days.

Disposal

Ask your pharmacist what to do with any << EMLA>> you have left over if your doctor tells you to stop using it, or you find that it has expired.

Product description

<< EMLA>> Cream contains the active ingredients lignocaine 25 mg/g and prilocaine 25 mg/g, plus:

carboxypolymethylene

polyoxyl hydrogenated castor oil

sodium hydroxide

purified water.

<< EMLA>> Cream
5 x 5 g tubes (with 10 dressings) or 30 g tube.
Marketed by:
AstraZeneca Limited
P O Box 1301, Auckland.

Ph: (09) 623 6300 or 0800 363 200.

Dated 19 March 2003

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Attorney Ref. No.: RC-572A
RICHARD C. DAVIS	Group Art Unit: 152
Serial No.: 07/388,735	Examiner: Webman
Filed: August 2, 1989	
For: BURN FOAM AND DELIVERY SYSTEM	

RULE 132 DECLARATION OF INVENTOR AS TO LONG FELT NEED AND AS TO EXPERIMENTS SUPPORTING APPLICANT'S ASSERTION THAT HIS FOAM HAS A MICELLE STRUCTURE WHICH IS STABILIZED BY A BIPOLAR ANTIBIOTIC HAVING A LINEAR STRUCTURE WITH ONE END BEING MORE HYDROPHILIC THAN THE OTHER

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Richard C. Davis, am the inventor in the above identified application. At a July 10, 1991 interview with the Examiner I mentioned there was a long felt need for my product and that others had tried to achieve my results. Further, I mentioned that my foam has a micelle structure that is stabilized by a bipolar antibiotic component. The Examiner asked at the interview that I file a declaration in support of these comments. This declaration is filed for that purpose.

My experience with my inventive foam began in the summer of 1984 when I was at Brook Army Hospital working with burn patients while in the Navy. I determined that there was a significant need for a water soluble product for treating burns

because the main product used at that time, silver sulfadiazine cream was difficult and painful for a patient to apply but was even more difficult and more painful for the patient to remove in that it was not water soluble. I contacted Marion Laboratories, which supplied the silver sulfadiazine cream we were using, and was told that Marion had spent years and millions of dollars attempting to develop a water soluble product containing silver sulfadiazine. It was told to me over the phone, by a gentleman whose name I cannot remember, that silver sulfadiazine, as a molecular entity, is biphasic having a hydrophilic end and a hydrophobic end. Because of this, I was told, it was impossible to get the chemical to dissolve in either a lipid solution solvent or in water. Sometime after that, I conceived the idea of trying to place the antibiotic (silver sulfadiazine) in a foam having a micellar-like bubble structure. After some minimal experimentation, I achieved some success by using greater than 50% water by weight in combination with one percent silver sulfadiazine and other components as are listed in my patent application. Although my experiments were originally intended only to produce a water-soluble foam, I was amazed at the stability of the foam I invented. In this regard, in order to determine the stability of the silver sulfadiazine molecule within the delivery foam, I developed multiple clinical experiments as follows:

The first experiment was to place my foam in an air conditioned room that was cooled to 65 degrees. I allowed the

foam to remain there for at least 24 hours. The foam showed no degradation, minimal desiccation, no leaching, no bleeding and no collapse over this 24 hour period.

In the second experiment I placed the foam into an extremely warm and humid environment, which was an indoor jacuzzi I left on steaming at 105 degrees for a period of 24 hours. Again there was no degradation of the foam cap, minimal desiccation, no leaching, no bleeding, and no collapse of a central bubble core.

In addition to these extreme experiments, I conducted multiple experiments at room temperature and normal humidity conditions and have achieved the same experimental results 100% of the time.

In order to verify the structure of my foam, I added a water soluble aniline dye to a slurry for making my foam prior to aerosolization and then produced a foam therewith, which I examined using a polarized lens under a lighted microscope. Using the microscope I observed a high degree of material in peripheral aspects of the bubbles of the foam and that none of the material had invaded the interior surface of the bubble. This indicated to me that I had in fact achieved a stable micellar structure with the silver sulfadiazine molecules, used as a "lock and key mechanism", being oriented perpendicularly (radially) throughout the very small bubble membranes with the water soluble ends thereof directed outwardly. I carried this analysis further applying thermodynamics to my aerosol structures. In this regard aerosol foams typically should collapse under varying conditions

of vapor pressure, temperature, humidity, solubility, pH and other factors; however, I have not observed this collapse, which typically occurs in other bubble aerosol systems, in my foam. From my dye experiment, I could see that a lipid soluble aerosol was confined in a space (bubble cavity) surrounded by a water soluble matrix. I could see from the experiment that the silver sulfadiazine acted as a "lock and key mechanism" by providing less random motion of the material which constituted the membrane of the bubble. In other words, the silver sulfadiazine appears to control the entropy of the system. If this were true, I reasoned, the addition of a small amount of water as a percentage by weight would cause an immediate collapse of my bubble structure due to the addition of hygroscopic pressure that would be produced by the additional water. In order to confirm this, I added a <u>small</u> amount of additional water and observed that this caused the bubble structure to disintegrate rapidly. I concluded from this that entropy was a factor in the stability of the microarchitecture of the bubble itself. By utilizing the "lock and key mechanism" of the silver sulfadiazine molecule, a linear, relatively straight, chain entity with a water soluble end and a lipid soluble end to provide a coupling at the gas/oil/water suspension interface (the wall of the bubble) and to reduce the mobility of those substances at that point, the stability of the foam has been experimentally observed to increase tremendously. This "locking" by the silver sulfadiazine molecule reduces the mobility of other substances at that point and therefore maintains

the integrity of the surface of the bubbles, i.e. the formation of stable bubbles. The fact that all of the thermodynamic factors contributing to bubble structure, that is, internal pressure of gas, external hygroscopic pressure of water and oil suspension, balance themselves very accurately in my foam to produce a stable bubble which does not expand after its initial expansion from the aerosol also lends support to my observation that there is a reduced molecular movement at the walls of the bubble. This, in turn, supports my position that my micellar foam has a reduced system entropy thereby creating a more stable oil-in-water slurry/gas propellant interface. This hypothesis was tested by using a 0.5% concentration of the silver sulfadiazine concentrated in my foam preparation and comparing the stability and solubility to my foam having the usual 1.0% mixture. The 1/2 percent compound was observed to be far less stable and required more water for bubble collapse to occur than did the one percent mixture.

Again these tests were conducted similarly to those mentioned on pages 2 and 3 of this declaration.

Finally, it is important that the materials within the water and oil suspension not be soluble in the propellant gas. Otherwise, the entropy reduction provided by the silver sulfadiazine would be overcome by a propensity of the propellant material to dissolve into the oil and water suspension. This would, again, produce what is seen in other aerosol foams of similar nature. That is, it would cause my foam to collapse,

disorganize, leach, or bleed. This would occur principally since water would be separated from the oil and water suspension as the propellant dissolved into the matrix of the foam itself.

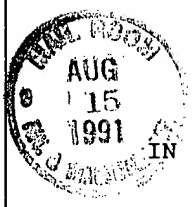
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____

Richard C. Davis

_____

Date



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	*	
	*	
RICHARD C. DAVIS	*	Atty. Ref. No.: RC-572A
	*	
Serial No. 07/388,735	*	Group Art Unit: 152
	*	
Filed: August 2, 1989	*	Examiner: Webman
	*	
For: BURN FOAM AND DELIVERY SYSTEM	*	

FIRST RULE 131 DECLARATION BY RICHARD C. DAVIS OF PRIOR INVENTION IN THE UNITED STATES TO OVERCOME THAU (4,981,677) CITED BY THE EXAMINER

Hon. Commissioner of Patents
and Trademarks
Washington, D. C. 20231

Sir:

I, Richard C. Davis, am the named inventor in the above identified application.

This declaration is to establish completion of the invention of this application in the United States at a date prior to September 23, 1987, which is the effective date of Patent 4,981,677, cited by the Examiner.

I hereby declare that I conceived and reduced the invention described in this application to practice prior to September 23, 1987 and as support thereof I attach the following documents:

1. A copy of a document entitled DRAFT PATENT BACKGROUND FOR SILVAFOAM, which I prepared prior to September 23, 1987.
2. A copy of a document entitled CLINICAL PROTOCOL FOR IN VITRO EVALUATION OF 1% SULFADIAZINE IN A NEW DOSAGE FORM---FOAM, again which I prepared prior to September 23, 1987.
3. A copy of a document entitled DERMA-FOAM CLINICAL PROTOCOL BY: RICHARD C. DAVIS JR. M.D. (date deleted).
4. Copies of two letters dated prior to September 23, 1987 (dates deleted) from AC Group to me.

The original of document 3 includes a date prior to September 23, 1987; however, this date has been blanked out as is allowed by MPEP Section 715.07.

Document 1 contains my description of the invention of this application which I prepared prior to Septemebr 23, 1987. It should be noted that under the heading "MANUFACTURING" this document states that I had made the product. I am sure this document predates September 23, 1987 because the enclosed dated letters (dates blanked) provide me with a frame of time.

Documents 2 and 3 are my descriptions of a protocol to be followed in testing my invention. Document 3 is dated on its face prior to September 23, 1987.

I actually reduced the invention described in document 1 to practice and ran tests with it prior to September 23, 1987.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Richard C. Davis

Date: 7/10/91

DRAFT PATENT BACKGROUND
FOR SILVAFOAM

This is to introduce a newly developed product - Silvafoam. The product's inventor is Dr. Richard C. Davis Jr. M.D. Silvafoam, as it is called, is an extrapolation of an earlier product - Silvadene which is produced by Marion Labs under US Patent 3,761,590 which expired May 17, 1987. Silvadene is a white thick cream used exclusively in the treatment of burns and abrasions. The product is one of the safest and most efficacious topical pharmaceuticals ever developed. It is stable and has a wide antimicrobial activity spectrum.

Silvadene is a compound composed of 9 substances. They are all readily available and none is exotic. The only active ingredient in the compound is Silver Sulfadiazine, a white crystalline powder antibiotic, which is very effective in the prevention of infection of injuries to the skin ie. burns and abrasions, especially Pseudomonas strains.

Despite its published literature and its patent claims to the contrary, Silvadene is both difficult and painful to apply. Because the Silvadene compound is very poorly water-soluble. It is even more difficult and painful to remove.

A burn is the most traumatic and severe injury that the human body can sustain and still survive. The major problem is that if the burn itself does not kill you, the infection that follows might. A burn removes the upper protective layers of the dermis and epidermis as well as disrupting the immunological barriers to infection. It retards regrowth of normal skin and promotes collagen formation which leads to scarring.

For the past 20 odd years Silvadene has been widely used as the medical treatment of choice worldwide for the treatment of burns to prevent infections. It has worked well but the following clinical problems are associated with it;

1. Time consuming application and removal,
2. Difficult application and removal,
3. Odor
4. Painful application and removal,
5. Excessive product waste and expense,

Silvafoam is a newly developed agent which is superior to Silvadene in ALL of these categories.

The new product is called Silvafoam. It is the first successfully foamed antibiotic compound ever made. Although foamed Silvadene was suggested in the Silvadene patent, no one has ever been able to successfully produce such a product until now. And as will be seen this

is no small feat. Silvafoam is a mixture of 11 substances, 9 of which are currently used in Silvadene. They are presented in percentages by weight, and the preferred embodiment of each is shown;

	Silvafoam	Silvadene
1. Silver Sulfadiazine	1.00 % *	1.00 %
2. White petrolatum	8.22 % *	16.43 %
3. Stearyl alcohol	8.22 % *	16.43 %
4. Isopropyl myristate	3.28 % *	6.57 %
5. Sorbitan monocleate	0.55 % *	1.10 %
6. Polyoxyl 40 stearate	4.38 % *	8.76 %
7. Propylene glycol	3.83 % *	7.67 %
8. Water	60.22 % *	41.74 %
9. Methylparaben	0.30 % *	0.30 %
10. Propane	5.00 %	
11. Isobutane	5.00 %	

* indicates Silvadene Component

The only active ingredient in each mixture is the Silver Sulfadiazine component. The only additional components contained in Silvafoam are the inactive, aliphatic, hydrocarbon, gaseous propellants which aerosolize the mixture and stabilize the foam's compact bubble architecture. But there is the addition of a critical amount of water in excess of the Silvadene product which will prove to be of critical importance further in this discussion. The other major change is the method of packaging.

FOAMS

A foam is not a simple structure. Each compound which is foamed must be able to sustain certain physical characteristics under the stress of forming a very thin curved surface containing an internal gaseous substance which dynamically interacts with the external gaseous environment and the atmospheric pressures encountered. The film surface is exposed to osmotic pressures, diffusion gradients, pH differences, temperature differences, and humidity differences. These along with the physical environmental stresses temperature, air flow, humidity, and others, will give each foam compound many of its characteristics. The chemistry of a foamed compound itself is also critical. Most foams work best when the compound is a suspension of water soluble and water insoluble components; a fact of great importance in the new product.

The chemical structure of Silver Sulfadiazine is such that the molecule tends to be linear rather than globular. One end is more hydrophyllic (water-loving) than the other. This fact makes it a "solubly polar" substance, with one end tending to be water soluble the other being virtually insoluble in water. The overall effect is that the compound is clinically poorly water soluble. A fact worth noting.

After much research and great expense, a formula and method of producing a stable foam with sustained antimicrobial activity and requisite application and solubility characteristics was produced. But a discussion of Micelle structure is now necessary.

MICELLES

A micelle is the fundamental structure of all living things. Basically a micelle is a hollow chamber surrounded by a surface (film, membrane, etc.) which utilizes physiochemical and electrochemical differences between the internal and external environments to create a stable architecture, facilitate transport of substances across the membrane, and many other complex functions. Picture a micelle like an inflated basketball, with the rubber skin acting like cell's membrane. Each living cell in our body is a micelle. Each is a dynamic little, hollow factory, specializing in some unique task for which it is designed. The big difference is that basketballs have air both on the inside and the outside of the skin which separates them. And good basketballs don't leak. Micelles, on the other hand, have a membrane which has little pores all over it designed for controlled leakage, both into and out of the cell.

The molecules which make up the membrane layer of micelles, tend to be linear in their geometry. Think of them like a wooden match having one end with a tail, the other with a head. Imagine that the thickness of the cell membrane is composed of an array of millions of these matches (molecules) all aligned and stuck together perpendicularly with their "heads" at one end on the outer surface facing away from the hollow chamber inside, and their "tails" at the other end pointing down into the hollow chamber. The interiors of most cells are "Hydrophobic", meaning they are water-hating. This means that the "tails" of the molecules which make up this membrane layer, contain fat-soluble compounds which do not mix well with water. The exterior surface ("heads") of the molecules contain "Hydrophyllic" or water-loving compounds which dissolve easily in water. The micelle membrane then acts like a barrier separating water-loving and water-hating environments and the complex chemical reactions which take place in both.

The chemical constituents of the Silvafoam mixture, combined with an appropriate amount of surface water, balanced by an appropriate internal (propellent) gas, mixed properly, at appropriate temperatures and pressures will allow for the formation of an architecture we commonly refer to as a "foam". Since the Silvadene mixture contains both hydrophyllic and hydrophobic components, it was recognized that if the proper balance could be found, it may be possible to, in essence, allow each bubble in the foam to form a stable micelle.

SILVAFOAM ARCHITECTURE

In order to be a commercial success, the search began for the proper combination of ingredients and processes which would allow the foam product to meet all of the following criteria;

1. It had to be inexpensive,

2. It had to have inactive ingredients except the antibiotic, which did not react with the other components.
3. It had to have pre-existing FDA approval of all components,
4. It had to be stable at the clinical level,
5. It had to have at least the same antimicrobial activity, and be no more toxic than Silvadene,
6. It had to be environmentally safe,
7. It had to be painless in application,
8. The bubble architecture had to have the water soluble portion on the outside, and the fat soluble portion of the compound on the inside.
9. It had to be resistant to desiccation.
10. It had to be easily removable with water,
11. The bubble size had to be correct.

The product as it now exists meets all of these criteria.

MANUFACTURING

It is amazing how simple the manufacture of the foam product actually turned out to be. Using the existing process for the making of Silvadene, (see Silvadene patent) and by changing the ingredients to the above percentages, stirring them together, heating them to 75 degrees and filling them into the aerosol cans at 35 pounds per square inch pressure using A-46 (85% propane and 15% isobutane) as the propellent; the foam product is formed. The secret is the use of the A-46 which acts to stabilize the bubble's interior and hold all of the Silver Sulfadiazine molecules' "tails" in place, along with the other foam components. The other secret is the use of a judicious amount of water which holds the "heads" of the molecules together, and allows for the entire foam to become clinically water soluble.

FUTURE EMBODIMENTS

This product has many applications for future EMBODIMENTS:

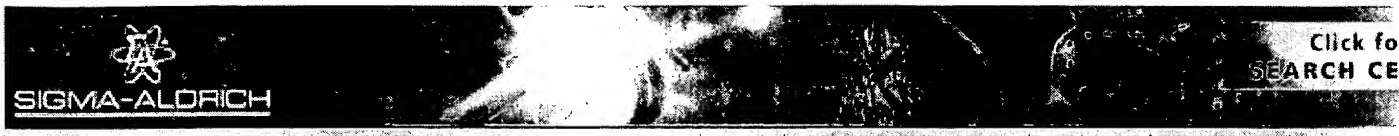
1. Over-the-counter preparations using non-prescription antibiotics like neosporin, bacitracin, neomycin, and others.
2. Addition of analgesics like Xylocaine, Benzocaine, and others.
3. Addition of enzymes like collagenase, lipase, elastase, etc.
4. Addition of steroid preparations like hydrocortisone, etc.
5. Addition of vitamins like A, E, B, etc.
6. Addition of hormones like growth hormone etc.
7. Addition of cofactors like biotin.
8. Addition of emollients like Aloe, Lanolin, and others.
9. Addition of Immunologic Agents, immunoglobulins, vaccines, etc.

CLAIMS

The claims section should be pretty straight-forward.

1. This is the first successfully foamed antibiotic.

2. This is the first stable foam of Silver Sulfadiazine.
3. It is inexpensive, painless, and spreads faster than a cream.
4 It is easier to use than bulky cream products.
5. There is no product waste with the foam.
6. The foam is clinically water soluble, washes off instantly, does not stain the skin, nor does it have a foul odor.
7. It is equally efficacious, providing the same broad antimicrobial spectrum as does Silvadene.
8. It has no more toxicity than does Silvadene.
9. It uses readily available materials, standard foam processing technology, and requires no special handling, refrigeration, or other precautions.



Product Number:**C8037**

Product Name:**Clobetasol propionate**

Product Information

Description / Pricing
Cert. of Analysis
Enter Lot No
Find
MSDS

Options

Print Preview
Bulk Quote
Ask A Scientist

SIGMA

Certificate of Analysis

TEST	LOT {SAMPLE} RESULTS
Product Name	Clobetasol propionate
Product Number	C8037
CAS Number	25122467
Formula	$C_{25}H_{32}ClFO_5$
Formula Weight	467.0
APPEARANCE	OFF-WHITE POWDER
SOLUBILITY	CLEAR COLORLESS SOLUTION AT 50 MG/ML IN CHLOROFORM
UV-VIS SPECTRUM	EMM = 15.6 AT LAMBDA MAX 239 NM IN ETHANOL
PURITY BY HPLC	100%
QC ACCEPTANCE DATE	OCTOBER 2000

David Feldker, Manager
Analytical Services